

Quantitative Risk/Benefit Analysis in Regulatory Decision Making

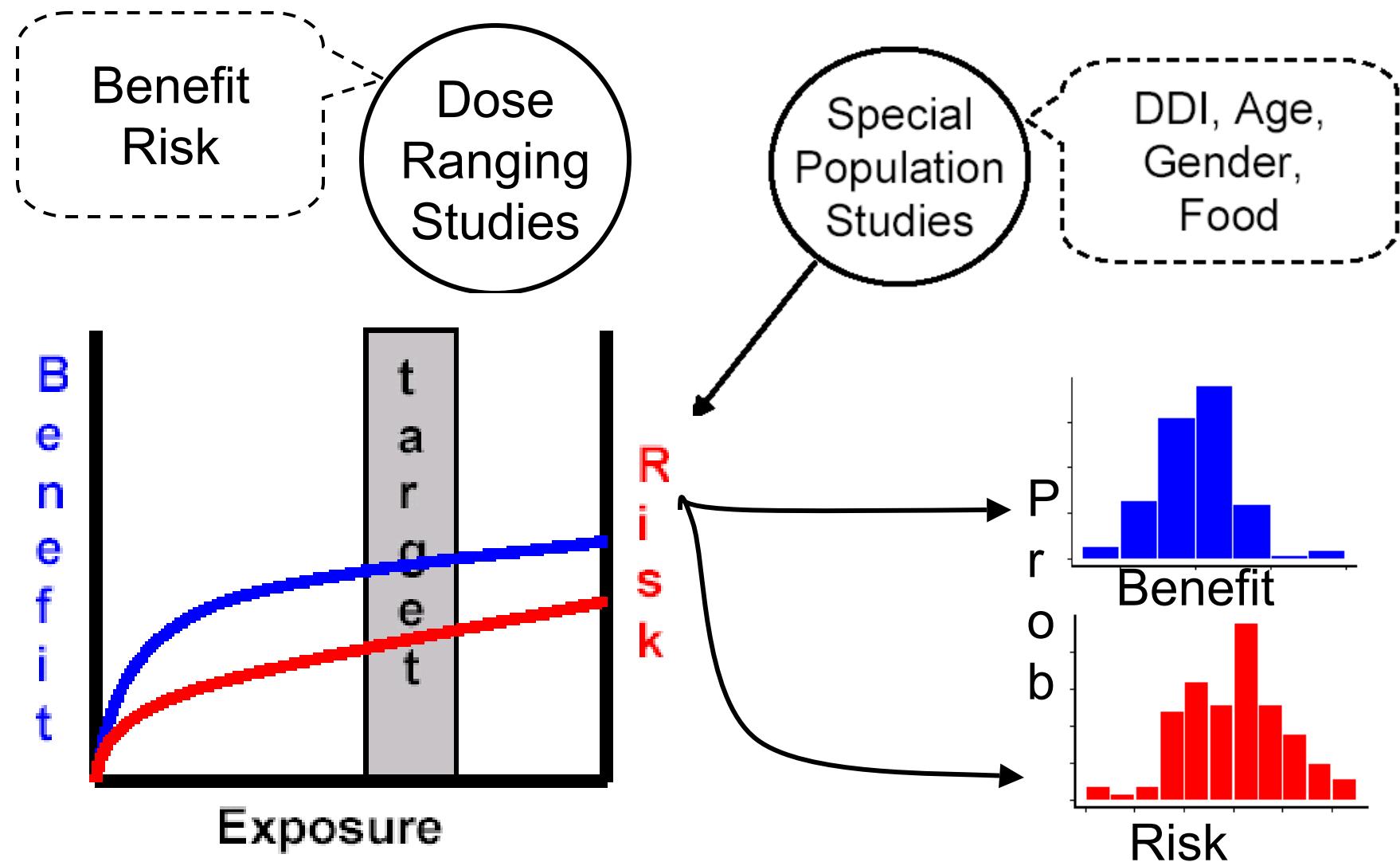
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FDA / CDER / OCPB / DPE 1

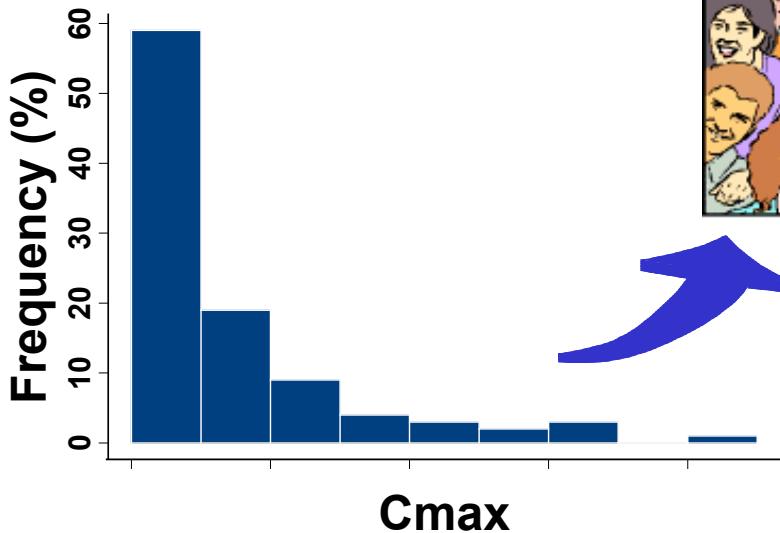
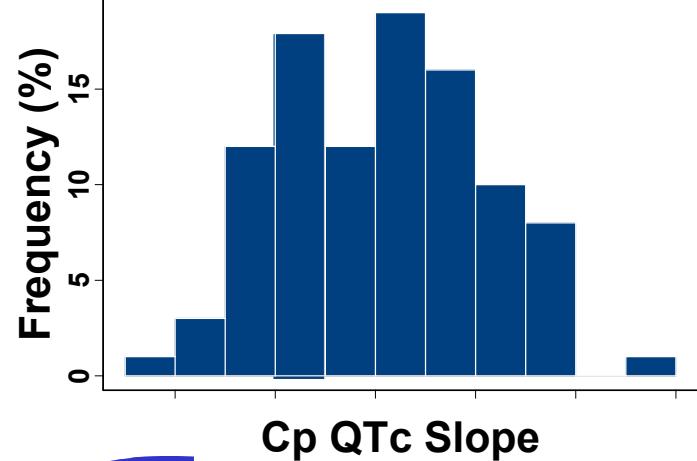
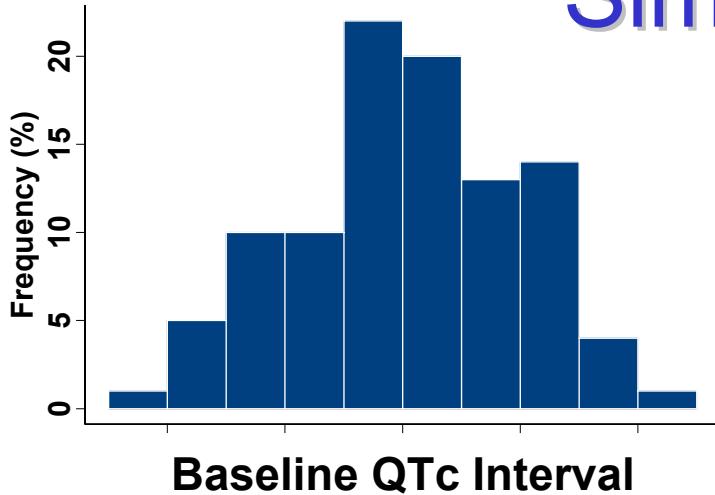
**Advisory Committee for Pharmaceutical Sciences
Clinical Pharmacology Subcommittee**

April 22, 2003

Integration of Knowledge



Simulations



Objective

- Quantitate the risk / benefit of a drug

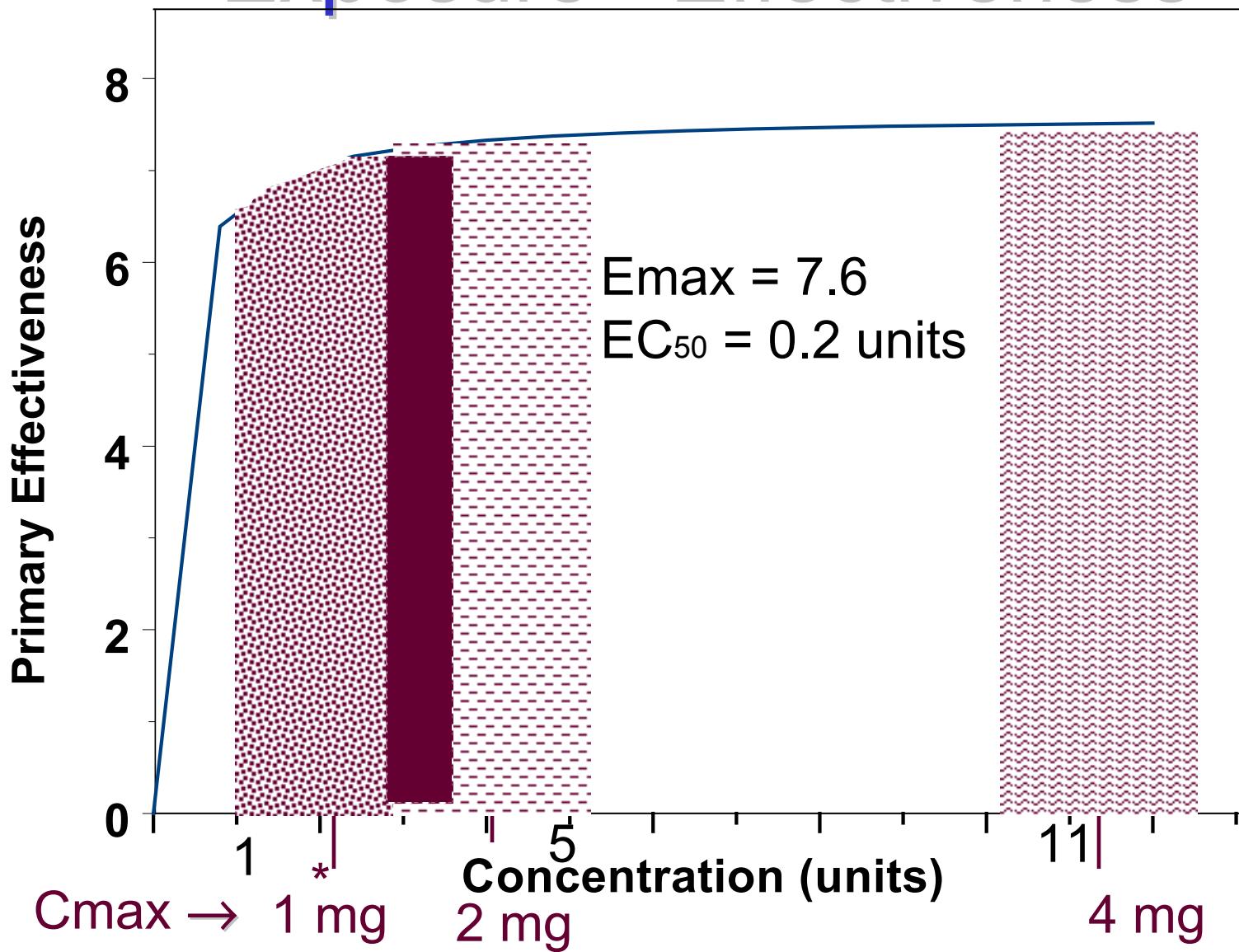
Exposure - Effectiveness Model

- Primary endpoint
- Largest clinical trial, longest duration
 - Primary effectiveness endpoint & PK collected @ week 0, 2, 4
- Nominal doses: 0.5 mg bid, 1, 2, 4 mg qd

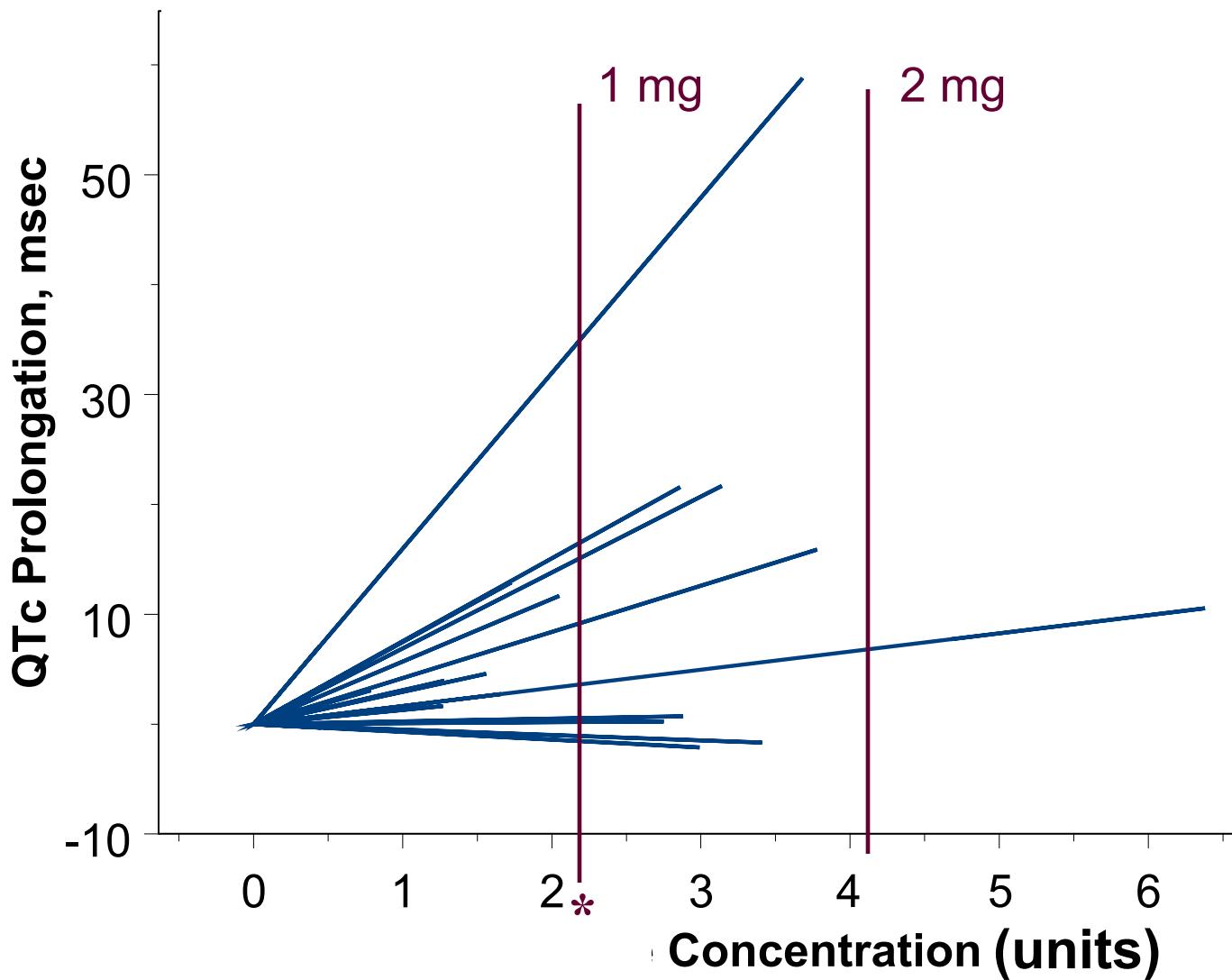
Exposure - Risk Models

- Adverse events
 - Data from all pivotal clinical trials
 - Focus on: dizziness, edema, liver toxicity, palpitations, tachycardia, vertigo
- ↑ QTc
 - Ketoconazole 400 mg + drug 0.5 mg qd
 - EKGs - 0, 1, 2, 3, 4 h post dose
 - Up to 24 h of drug PK

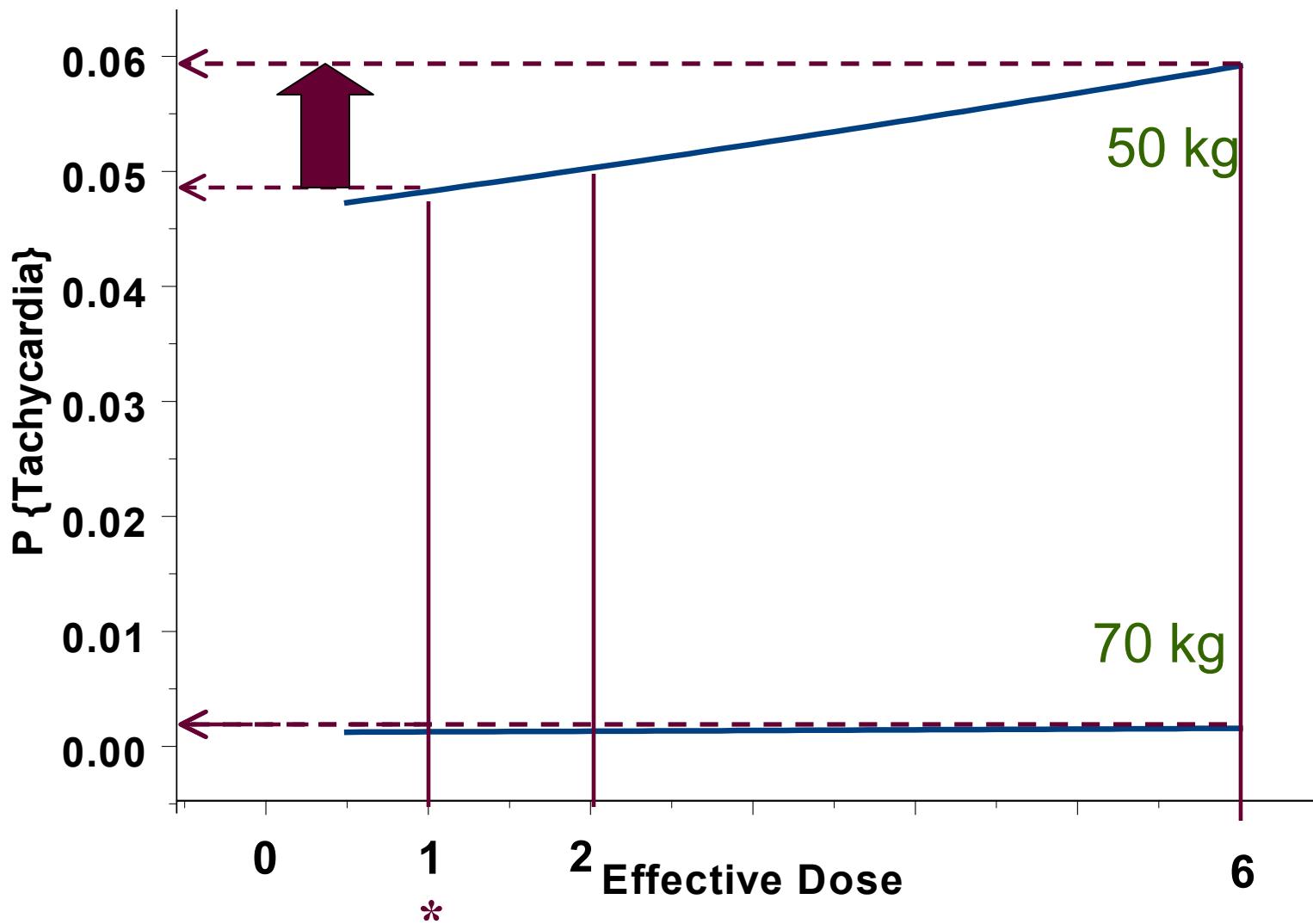
Exposure - Effectiveness



Exposure - QTc Prolongation



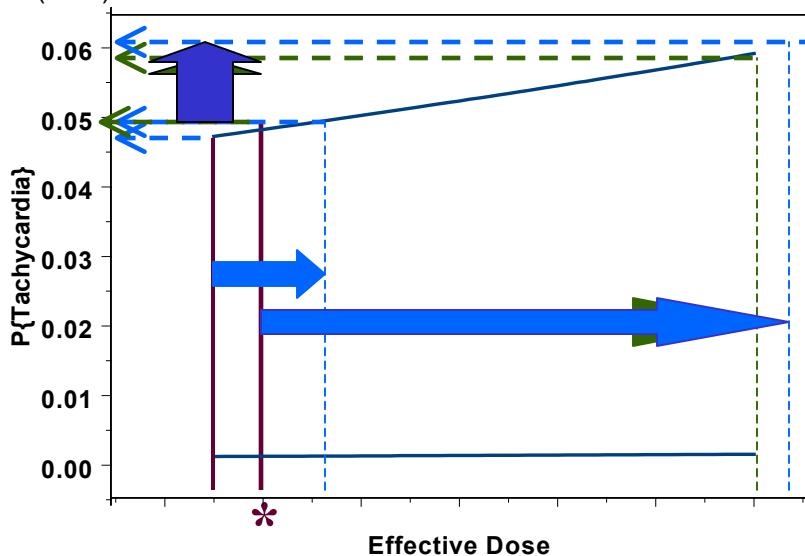
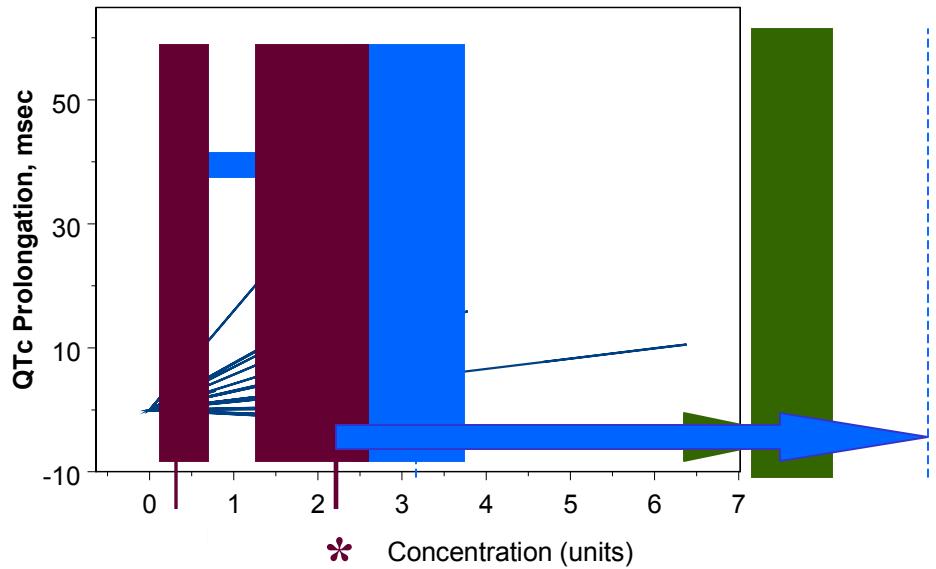
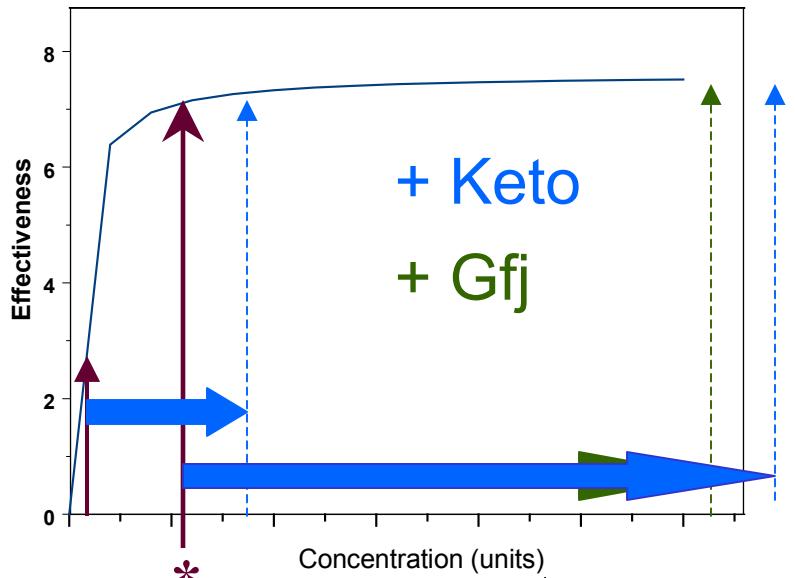
Probability of Tachycardia



Special Population Studies

| Prognostic Factor | Results |
|---------------------------|---------------------------------------|
| Ketoconazole 400 mg qd | AUC = 13 - fold ↑ Cmax = 7- fold ↑ |
| Grapefruit Juice | AUC = 7- fold ↑ Cmax = 6 - fold ↑ |

Integration of ER Relationship



Summary of Data Integration

| Prognostic Factor | Exposure | Response |
|------------------------------|--------------------------------------|--|
| Ketoconazole + 0.5 mg | AUC = 13- fold ↑ Cmax = 7- fold ↑ | Effectiveness: + 4 Δ QTc: 5% of population have ↑ QTc > 32 msec Tachy: ↔ |
| Grapefruit Juice + 1.0 mg | AUC = 7- fold↑ Cmax = 6-fold ↑ | Effectiveness: ↔ Δ QTc: ? Tachy: ↑ 1 % in 50 kg pt |
| Ketoconazole + 1.0 mg | AUC = 13- fold ↑ Cmax = 7-fold ↑ | Effectiveness: ↔ Δ QTc: ? Tachy: ↑ 1 % in 50 kg pt |

Conclusions

- Weigh effectiveness and risks with review team
 - Know assumptions of models
- Recommend conduct appropriate QT study
 - Explore wide concentration range
 - Collect QT data over 24 h